

## **REMARKS**

### **Status of Claims**

Prior to the present amendment, claims 1-59 were pending. Without prejudice or disclaimer, claims 50, 51, 53, 54 are cancelled herein.

Further, claim 1 is amended to incorporate the limitations of claims 50, 51 and 53. Specifically, claim 1 is amended to recite that the inner, continuous layer consists of one or more lipids selected from: vegetable oils, hydrogenated vegetable oils, and mixtures thereof. As a result of the above amendment, claim 52 is also amended. Thus, no new matter is introduced.

### **Rejections under 35 U.S.C. § 103(a)**

#### **A. Iijima et al in view of Riga et al.**

The Examiner rejects Claims 1-8, 22-40 and 46-56 under 35 U.S.C. § 103(a) as being unpatentable over Iijima et al in view of Riga et al. According to the Examiner, Iijima et al teach a granular composition containing choline for a ruminant, which would be "capable of reaching an abomasum and downstream thereof substantially in the form of granules, without easily dissolved or decomposed in the rumen" (the so called "by-pass properties"). According to the Examiner, Iijima et al do "not expressly teach the overcoating of the choline chloride comprising an outer layer of carnauba wax and an inner layer of a hydrophobic substance". However, according to the Examiner:

"[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition of choline chloride in the core, coated with hydrophobic materials such as carnauba wax and hydrogenated oils, as suggested by Iijima, and specifically overcoating the first layer by an outer or second layer or retardant by using carnauba wax, as suggested by Riga, and produce the instant invention." (see page 7, 4th paragraph, of the outstanding Office Action).

Applicants respectfully traverse this rejection because the Examiner has failed to establish a *prima facie* showing of obviousness. Particularly, the Examiner has simply picked up some specific features from different references and combined them arbitrarily having as guidance the knowledge of applicant's disclosure. This clearly resorts to "hindsight" which must be

avoided when assessing unobviousness. To make a fair determination whether the claimed invention as a whole would have been obvious, the prior art references relied upon must be considered in its entirety, i.e. as a whole, including portions that would lead away from the claimed invention.

Iijima et al disclose a granular composition for ruminant containing as a main component choline or a physiologically acceptable derivative thereof. The granular composition is prepared by: (i) granulating the choline or its derivative having a specific granular size (see col. 2, lines 17-19, of Iijima et al), an excipient having a specific granular size (see col. 2, lines 20-21, of Iijima et al), and an hydrophobic binder, by using an agitation granulator; (ii) after cooling, separating and classifying the resultant granules to obtain spherical granules having a specific size (see col. 2, lines 25-27, of Iijima et al), forming a thin film on said granules at specific process conditions (see col. 2, lines 28-34, of Iijima et al) by adding 20-40 parts by weight of a heated molten mixture of a hydrophobic overcoating agent and a solubility modifier.

As excipient, it is used magnesium oxide or a mixture of magnesium oxide with various inorganic salts or oxides (see col. 2, lines 58-68, of Iijima et al). As hydrophobic binder, compounds having a melting point of 40°C to 100°C may be used, such as hydrogenated fats or oils, waxes and the like; among waxes, carnauba wax is suggested (see col. 3, lines 23-40, of Iijima et al).

As hydrophobic overcoating agent, the same products indicated above as hydrophobic binders may be used (see col. 3, lines 50-56, of Iijima et al). As solubility modifier, various inorganic salts, oxides, or hydroxides may be used (see from col. 3, line 62, to col. 4, line 3, of Iijima et al).

Therefore, the teaching derivable from Iijima et al is that a so-called rumen-bypass granular agent can be obtained by producing a core comprising choline or a derivative thereof, an excipient (magnesium oxide or the like) and a hydrophobic binder (e.g., *inter alia*, a hydrogenated fat or oil, or carnauba wax), and by coating said core with a layer of a hydrophobic overcoating agent (e.g., *inter alia*, a hydrogenated fat or oil, or carnauba wax) and a solubility modifier (e.g. an oxide).

Therefore, Iijima et al do not disclose a rumen-bypass granular agent where a core containing choline chloride is coated by two different layers: an inner layer consisting of one

or more lipids selected from: vegetable oils, hydrogenated vegetable oils, and mixtures thereof, and an outer continuous layer mainly consisting of carnauba wax. Contrary to the solution provided by the present invention, Iijima et al equates, as hydrophobic agents to be used equally in the core and/or in the sole outer layer, hydrogenated fats or oils and carnauba wax.

The superior results of the rumen-bypass granular agent according to the present invention are shown in the examples provided in the application as filed (see Examples 1-5 according to the invention, in comparison with Commercial Products 1-2 and Controls 1-3). For ease of comparison, we are reporting hereinbelow a table with the compositions of the cores and of the coatings for Examples 1-5 and for Controls 1-3:

	Inner coating layer	Outer coating layer	Single coating layer
Example 1	Hydrogenated palm oil	Carnauba wax + Soybean oil	---
Example 2	Hydrogenated soybean oil	Carnauba wax	---
Example 3	Hydrogenated soybean oil	Carnauba wax	---
Example 4	Hydrogenated soybean oil	Carnauba wax + Palm oil	---
Example 5	Hydrogenated soybean oil	Carnauba wax + Palm oil	---
Control 1	---	---	Hydrogenated palm oil
Control 2	---	---	Carnauba wax
Control 3	---	---	Carnauba wax + Hydrogenated palm oil

Tables 1, 3 and 5 of the specification report the by-pass properties of the working Examples 1-5 and of Controls 1-3, both of the granular products as such, and of the granular products when mixed and maintained in contact with different feed formulations for ruminants. By comparing the above data, it is apparent that the granular products according to the present invention show excellent by-pass properties. Moreover, said properties are maintained at very high levels even after a long time in the feed formulations, while the granules of Controls 1-3, put in the same conditions, show a remarkable degradation of their by-pass quality. These results are of the outmost importance for a practical use of choline granular products as supplements for the diet of ruminants. The granules according to the present

invention can be admixed and maintained for a long time in standard feed formulations, while the granular products according to the prior art, maintained in the same conditions, show an unacceptable deterioration of the by-pass properties.

The Examiner relies upon the secondary reference, Riga et al, to allegedly cure the deficiencies of the primary reference, Iijima et al. Applicants respectfully disagree at least for the following reasons.

Firstly, a person skilled in the art would not have considered Riga et al as a reference that could give any hints to cure the deficiencies of Iijima et al. As already explained in our previous response to the second Office Action, Riga et al relates to anti-stress, anti-impairment and anti-aging drug in form of capsules or film-coated tablets, which may be gastrosoluble or enterosoluble. As active principles, choline or derivatives thereof are not even suggested (see col. 5, lines 20-37, of Riga et al).

The capsules or tables are intended for human consumption, namely for monogastric animals (see col. 21, lines 39-41, of Riga et al). As already explained in our previous response, the conditions in a ruminant digestive system are much harsher than those in a monogastric animal. Therefore, no one skilled in the art would have considered Riga et al as a relevant reference to find a solution for granular composition containing choline to be used for feeding ruminants having improved by-pass properties, particularly when maintained for a long time in contact with ruminant feed formulations.

This is confirmed by the example of enterosoluble units given by Riga et al., particularly the example reported at col. 9, lines 11-41, which the Examiner refers to in the outstanding Office Action. According to that example, timed-release granules of nicotinic acid are prepared by using two retarders, namely ethyl cellulose and carnauba wax. Firstly, the only component in common with the present invention is carnauba wax, while the first retarder is ethyl cellulose, which is clearly excluded from claim 1 as newly amended. It is worth noting that ethyl cellulose would be totally unsuitable as coating for rumen-bypass granular agents containing choline chloride as active principle at least for the following reason. In fact, choline chloride is remarkably hygroscopic and ethyl cellulose cannot constitute an effective barrier against humidity since it has a high affinity for water. When placed in a humid environment, ethyl cellulose swells and releases water to the underlying materials, especially when the latter are highly hygroscopic such as choline chloride.

Moreover, by carefully reading the process for preparing the above granules of Riga et al, one skilled in the art cannot derive that the resulting granules are actually coated by two different continuous layers. In fact, at col. 9, point a) I), it is disclosed that nicotinic acid mixed with aerosil and polyvinylpyrrolidone is added with a solution of ethyl cellulose and diethyl phthalate in suitable solvents. Then "[t]he mass thus obtained is granulated through the sieve 10 [...]". Then, a solution of carnauba wax in suitable solvents is added and the resulting mixture is again granulated. Such a process cannot provide granules continuously coated by two different layers of the two different retarders. It is apparent that to obtain a uniform coating of granules, the components of the core must be firstly granulated and then coated by the retarder. Granulation carried out after mixing the core components with the retarder cannot provide an actual coating, but simply a mixture of the core with the retarder.

The only reference in Riga et al to enteric coating is given from col. 10, line 8, to col. 11, line 5, where, however, the coating is a single coating by means of retarders totally different to those according to the present invention.

Therefore, Applicants respectfully submit that the above rejection over Iijima et al in view of Riga et al is in error and should be withdrawn.

**B. Iijima et al in view of Riga et al and further in view of Richardson.**

The Examiner rejects Claims 9-14 and 57-59 under 35 U.S.C. § 103(a) as being unpatentable over Iijima et al in view of Riga et al and further in view of Richardson.

The Examiner alleges that it would have been obvious to modify the core of the claimed granules by adding as flow modifier a silicate as suggested by Richardson (see col. 10, lines 11-13).

This rejection is clearly overcome as far as the arguments set forth above against the combination of Iijima et al with Riga et al are accepted and convince the Examiner that the above main rejection A. is untenable.

**C. Iijima et al in view of Riga et al and further in view of Brommelsiek et al.**

The Examiner rejects Claims 15-19 and 41-42 under 35 U.S.C. § 103(a) as being unpatentable over Iijima et al in view of Riga et al and further in view of Brommelsiek et al.

The Examiner alleges that it would have been obvious to modify the core of the claimed granules by adding a lubricant such as stearate salts as suggested by Brommelsiek et al (see e.g. col. 7, lines 17-25, 26-27, 46-49).

This rejection is clearly overcome as far as the arguments set forth above against the combination of Iijima et al with Riga et al are accepted and convince the Examiner that the above main rejection is untenable.

**D. Iijima et al in view of Riga et al and further in view of Richardson and Brommelsiek et al.**

The Examiner rejects Claims 20-21 and 43-45 under 35 U.S.C. § 103(a) as being unpatentable over Iijima et al in view of Riga et al and further in view of Richardson and Brommelsiek et al.


This rejection is clearly overcome as far as the arguments set forth above against the combination of Iijima et al with Riga et al are accepted and convince the Examiner that the above main rejection is untenable.

**Conclusion**

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

If any additional fees are required by this communication, please charge such fees to our Deposit Account No. 16-0820, Order No. BUG5-36500.

Respectfully submitted,  
PEARNE & GORDON LLP

By   
John P. Murtaugh, Reg. No. 34226

1801 East 9<sup>th</sup> Street  
Suite 1200  
Cleveland, Ohio 44114-3108  
Phone: (216) 579-1700  
Fax: (216) 579-6073

Date: Nov. 14, 2008